

Deep sequencing of circulating tumor DNA for personalized lung cancer detection and radiotherapy response monitoring



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Circulating tumor DNA (ctDNA) represents a promising biomarker for sensitive, specific, and dynamic detection of disease burden in cancer patients. Mutations in tumor-derived DNA represent ideal potential biomarkers since they are highly specific to tumor cells and involved in disease pathogenesis. However, even in advanced cancer patients, concentrations of ctDNA are often very low and therefore difficult to detect. We have developed a novel, ultra-sensitive and specific method for detection of circulating tumor DNA called Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq). This method was developed specifically for detection of ctDNA in non-small cell lung cancer patients, although it is broadly applicable to other cancer types. In this presentation I will describe recent improvements to CAPP-Seq that further improve the sensitivity of the assay, with a focus on applications of ctDNA analysis in lung cancer patients treated with radiotherapy.

Circulating tumor cell eXplants (CDX) to advance small cell lung cancer (SCLC) research and drug development



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SCLC accounts for ~15% of all lung cancer cases and ~220,000 deaths annually worldwide. Although response rates to first line platinum-based chemotherapy are high (~80%), progression free survival in most patients is short (3-12 months) due to the development of chemotherapy resistance and progressive disease. In addition, approximately 20% of SCLC patients are classified as chemorefractory with progressive disease within 3 months of their initial treatment. The lack of durable chemotherapy responses contributes to the poor prognosis in SCLC; with a 5 year survival rate of ~5% (5,6). Platinum based chemotherapy regimens have remained the same as standard of care for SCLC for the past 30 years. Targeted therapies have yet to make impact on patient outcomes, although several ongoing clinical trials of

small molecular and immunotherapies begin to show promise.

The majority of SCLC patients present with metastatic disease and < 5% patients are suitable for resection with curative intent. Biopsies of SCLC are generally challenging, often providing a low quantity and quality of specimen for research purposes: specimens are usually necrotic and exhibit crush artefact. Serial biopsy in SCLC is rare. Understanding the biology of drug resistant, advanced and progressive disease is hampered by limited clinical specimens to study. In SCLC, CTCs detected by the EpCAM dependent CellSearch platform are prevalent, CTC number is prognostic for overall and progression free survival, the dynamic range is sufficient to use CTC number as a pharmacodynamic biomarker and predictive CTC based biomarkers are feasible. Marker independent CTC enrichment platforms reveal the presence of EpCam negative SCLC CTCs. To address the paucity of SCLC biopsies for research, we recently developed Circulating Tumour Cell patient Derived eXplant models in immune-compromised mice (CDX, Hodgkinson et al, Nature Medicine, 2015).

I will describe our SCLC CDX panel derived from chemosensitive and chemorefractory patients at baseline and CDX matched pairs at baseline and progression. The CDX models tested to date mirror patient responses to standard of care chemotherapy. These models are being exploited to search for new drugable targets, to test targeted treatments and to interrogate treatment resistance mechanisms. As few as 10 SCLC CDX cells can recapitulate the CDX tumour suggesting a high frequency of SCLC 'stem-like' cells. We also discovered that a subset of SCLC CTCs exhibit vasculogenic mimicry, a 'stem-like' angiogenic switch whereby tumour cells form their own blood vessel walls. The clinical relevance of this biology is under investigation using CDX and xenograft models. We hypothesize that VM facilitates dissemination, but may also enhance drug delivery and alleviate hypoxia. In summary, our SCLC CDX models of metastatic lung cancer offer new avenues to study biology, mechanisms of tumor cell dissemination.

Immunotherapy in small cell lung cancer



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Small cell lung cancer (SCLC) is a high-grade neuroendocrine malignancy that accounts for approximately 15% of all lung cancers in the United States. Patients with metastatic disease have a median survival of less than one year, and despite a large number of early phase